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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,576	11/02/2006	Etienne Jacotot	BJS-1721-112	5093

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EXAMINER	
GUPTA, ANISH	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,576	JACOTOT ET AL.	
	Examiner	Art Unit	
	ANISH GUPTA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-24-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

1. Claim 1 is objected to because of the following informalities:

In claim 1, the definition of X2 should be changed to avoid any unnecessary confusion. Applicants should state that X2 is either a C, in which case X4 is a C and the X2 and X4 are connected by a disulfide bridge, ... Appropriate correction is required.

In claim 2-3, 5-6 the claims recite "peptide of claim 1 [or 5], characterized in that." Applicants should avoid using characterized, since the sequence claims is not a characteristic. Applicants should state "The peptide of claim 1 having the sequence" or "The peptide of claim 5 comprising the sequence of SEQ ID NO 12 to SEQ ID NO 23."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-12 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c).

Note the explanation given by the Board of Patent Appeals and Interferences in Ex parte Wu, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by "such language" is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of Ex parte Steigewald, 131 USPQ 74 (Bd. App. 1961); Ex parte Hall, 83 USPQ 38 (Bd. App. 1948); and Ex parte Hasche, 86 USPQ 481 (Bd. App. 1949).

In claim 1, for the definition of X1, the claim recites the amino terminal end of the G or GG is free, alkylated, acylated or in **particular** acetylated, or contains a labeling group, **such as** biotinyl group. This claim language also appears for the definition of X2, X5 and X9 and is also used in claims 3-4.

In claim 1-3, for the numerous X variables, the claims recite that the variable is a "motif." For example, for X3, the claim states that X3 can be either an M motif or a norleucine motif. Motif is undefined. It is unclear if motif, as used in the claim, refers to the specific amino acid only, a portion of the amino acid, or a mimic that functions similar to the amino acid as claimed. If the former is true, then Applicants should delete the word motif to avoid confusion. If the other definitions are intended, then it is unclear what portions of the amino acid are considered to be motifs or what mimics can be deemed to function similar the amino acids claimed and thus are motifs.

In claim 1, for X2 and X4, the claim state that X2 or X4 are defined as "amino acid bearing an acidic group such as A or D." However, A, using the single letter international code, is Alanine which does not contain an acidic group.

In claim 1, for variable X5, it is unclear how many amino acids compose the "di, tri, tetrapeptide motifs." The claims state that the motif is composed of "two di-, tri-, or tetrapeptide motifs composed of G or a combination of G and of S." The claim then goes on to say "such as GG, GGG, GGGG, GGS, GGGS or GGSGGS." It is unclear from the claims if the motifs are only GG, GGG, GGGG, GGS, GGGS or GGSGGS or are much larger including hexamers and octomers. Two tetrapeptide motifs of GGGG would be GGGGGGGG. Furthermore, a "succession of di-[peptide]" would lead to at least a tetrapeptide motif. Thus, it is unclear how GG, GGG or GGS can be achieved. Finally, it is unclear from the claim, if in the "two di-, tri-, or tetrapeptide motifs" the two motifs have to be the same or if they can be different.

In claim 3, the use of "and/or" is confusing. It is unclear if all of the modification are required by the claim or only some. It more difficult to interpret the claim since the claim recites "in particular" prior to alkylated group. Thus it is unclear if only alkylation is desired or any other modification recited in the claim.

Claim 3 recites the limitation "the native peptide" in Claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim s 11-12 provides for the use of peptides, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 11-12 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte*

Dunki, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 5 does not seem to further limit base claim 1. Claim 5 claims a peptide of the sequence X-R-G-D-M-F-G-X. This implies that the N- and C- terminal end is open to any amino acid. However, claim 1 requires specific amino acid substitutions on the N- terminal end, X1, and C- terminal end, X5-L-L-F . . . It is unclear form claim 5, if the limitations of claim 1 are required. Note that claim 5 and 6 do not require the presence of X2 and X4.

Claim 5 and 6 recites the limitation "X" and "X'" in 5. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 7-12 rejected under 35 U.S.C. 103(a) as being unpatentable over Edelman et al. (WO02061105) in view of Hart (WO01/92542).

The claims are drawn to peptides with antiangiogenic activity.

Edelman et al. teach HIV-1 protein Vpr induces mitochondrial membrane permeabilization via its physical and function interaction with the mitochondrial inner membrane protein ANT (see page 8) The reference further teaches a complex that comprises a cytotoxic molecule and a targeting molecule able to target cells. The targeting/cytotoxic molecule exhibits selective toxicity against angiogenic endothelial cells and tumor cells(see page 9). As a Tox (cytotoxic agent) portion of the complex, the reference disclose the peptide HFRIGCRHSRIG, HFKIGCKHSKIG, DTWTGVEALIRILQQLLFIHFRIGSRHSRIGHQQRRTRNGASKS (see page 10). The reference disclose that the C-terminal moiety (Vpr52-96), within an .alpha.-helical motif of 12 amino acids (Vpr71-82), contain several critical arginine (R) residues (R73, R77, R80), which are strongly conserved among different pathogenic HIV-1 isolates. Thus, the pro-apoptotic portion (pTox) of the chimeric polypeptide of the invention can contain, for example, the sequence HFRIGCRHSRIG (HIV-1 Vpr71-82), HFKIGCKHSKIG, Vpr 71-96, Vpr 52-96, or a pseudo peptidic variant such as D[HFRIGCRHSRIG] (see page 13-14). The reference also states using a yeast model system, it has been confirmed that there is a cytocidal activity associated with the C-terminal portion of Vpr, particularly the sequence HFRIGCRHSRIG. Vpr and portions of Vpr containing the sequence HFRIGCRHSRIG can kill a range of mammalian cells including human lymphocytes (see page 13). Thus, the reference teaches that the minimum sequence required for cytotoxic activity is HFRIGCRHSRIG. Note that the native sequence form HIV-1 viral protein R (Vpr) has the sequence

MEQAPEDQGPQREPYNEWTLELLEELKSEAVRHFPRIWLHNLGQHIYETYGDTWAGVE

AIIRILQQLLFI**HFRIGCRHSRIG**VTRQRRARNGASRS (see page 13). This sequence contains the claimed fragments of LFIHRIGSRHSRIG.

The difference between the prior art and the instant application is that the reference does not specifically teach the use of RGD peptides are targeting agents.

However, Hart teaches that RGD peptides can serve as ligands for vectors since they bind to integrins with high affinity (see pages 2-3). The reference disclose that sequence a peptide that contains the consensus sequence CRGDMFGC may be used an integrin binding peptide (page 5, lines 22-27) The reference exemplifies the peptide GGRGDMFGC and teaches that it has an affinity for integrin αv and α5β1 (see page 7). The reference also disclose the peptide CRGDMFGCGG (see page 9). The reference disclose that a spacer, comprising the dipeptide GG, can be present on the peptide to improve transfection efficiency (see page 7). The reference disclose for the CRGDMFGCGG a spacer may be linked to the N-terminal of the peptide (see page 9) The reference discloses the use of the peptide as targeting agents for carrying nucleic acids, which can encode a protein, to treat various cancers (see page 21). In summary, Hart teaches peptides having the sequence CRGDMFGC that target integrins and can be used to carry therapeutic agents.

It would have been obvious to one of ordinary skill in the art to use an integrin binding peptide as a targeting agent in a complex with a peptide containing HFRIGCRHSRIG, because CRGDMFGC recognizes integrins and has been shown to deliver therapeutics for the treatment of cancer. It would have been obvious to use the dipeptide GG on the terminal ends of CRGDMFGC because the di peptide improves transfection efficiency. Finally, it would have been obvious to use any peptide from

MEQAPEDQGPQREPYNEWTLELLEELKSEAVRHFPRIWLHNLGQHIYETYGDTWAGVE

AIIRILQQLLFI**HFRIGCRHSRIG**VTRQRRARNGASRS

because the peptide HFRIGCRHSRIG is the minimum sequence necessary for cytotoxic activity.

Note that the use claims have been interpreted as method of making claims, since the claims recite use of peptides for "producing" medicaments. Since the obviousness rejection sets forth how to make the claimed complex, the rejection meets the limitations of the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (571)272-0965. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can normally be reached on (571) 272-0562. The fax phone number of this group is (571)-273-8300.

/Anish Gupta/
Primary Examiner, Art Unit 1654